CHEMICALS UNDER CONSIDERATION FOR POSSIBLE LISTING VIA THE AUTHORITATIVE BODIES MECHANISM

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The chemicals listed in Tables A and B below may meet the criteria for listing under Proposition 65 via the authoritative bodies listing mechanism. The regulatory guidance for listing by this mechanism is set forth in Title 22, California Code of Regulations (CCR), Section 12306. For example, the regulations include provisions covering the criteria for evaluating the documentation and scientific findings by the authoritative body to determine whether listing under Proposition 65 is required.

For reproductive toxicity, the US Environmental Protection Agency (US EPA), US National Institute of Occupational Safety and Health (NIOSH), International Agency for Research on Cancer (IARC; for transplacental carcinogenicity only) and Food and Drug Administration (FDA) are authoritative bodies. For carcinogenicity, the authoritative bodies are US EPA, IARC, FDA, NIOSH and the National Toxicology Program (NTP). Chemicals which have been identified as causing cancer or reproductive toxicity are given in the tables below. OEHHA has found that these chemicals appear to be "formally identified" as causing these effects according to the regulations covering this issue (22 CCR 12306[d]): The chemicals below are the subject of reports published by the authoritative bodies which conclude that the chemicals cause cancer or reproductive toxicity or have been included on a list of chemicals causing these effects issued by the authoritative body. Also, the documents specifically and accurately identify the chemicals and the documents meet one or more of the criteria outlined in 22 CCR 12306 (d)(2).

OEHHA also finds that the criteria given in regulation for "as causing cancer" (22 CCR 12306[e]) or "as causing reproductive toxicity" (22 CCR 12306[g]) appear to have been satisfied for the chemicals in the tables below. In making this evaluation, OEHHA relied upon the discussion of data by the authoritative bodies in making their findings that the specified chemicals cause such effects. A brief discussion of the relevant carcinogenesis and reproductive toxicity studies providing evidence for the findings is presented below. The statements in bold reflect data and conclusions that appear to satisfy the criteria for the sufficiency of evidence for carcinogenicity (22 CCR 12306[e]) or reproductive toxicity (22 CCR 12306[g]).

Table A. Chemicals Under Consideration for Possible Listing as Carcinogens

Chemical	CAS No.	Chemical Use	Reference
Chloroprene	126-99-8	Intermediate in production of polychloroprene elastomer (used in coating of rubber goods, wire, cable, fabric; cements, sealants, adhesives).	NTP (1996a, 1996d)
Cobalt sulfate heptahydrate	10026-24-1	Used in electroplating and electrochemical industries; in inks, paints, varnishes, linoleum; ceramics; in animal feed; has been used on pasture lands.	NTP (1996b, 1996d)
Fenoxycarb	72490-01-8	Carbamate insecticide acts as an insect growth regulator; used primarily in structural pest control.	US EPA (1996a)
Oxythioquinox	2439-01-2	Insecticide and fungicide used on apples, apricots, citrus, pears; walnuts.	US EPA (1996b)
o-Phenylphenol	90-43-7	Germicide and fungicide used on citrus fruits and vegetables	US EPA (1994a)
Primidone	125-33-7	Anti-epileptic drug (phenobarbital analogue).	NTP (1996c, 1996d)
Thiodicarb	59669-26-0	Carbamate insecticide used on cotton, soybeans, corn, broccoli, cabbage, leafy vegetables, and tomatoes.	US EPA (1996c)
Vinclozolin	50471-44-8	Fungicide used on various flowers, vegetables, berries and stone fruit to control molds.	US EPA (1996d)

Table B. Chemicals Under Consideration for Possible Listing as Causing Reproductive Toxicity

Chemical	CAS No.	Toxicological Endpoints	Chemical Use	Reference
Di(2-ethylhexyl) phthalate (DEHP)	117-81-7	developmental toxicity male reproductive toxicity	Softener for plastics	NIOSH (1990)
2,4-Dinitrotoluene	121-14-2	male reproductive toxicity	Used in organic synthesis and manufacture of dyes and explosives	US EPA (1986a)
2,6-Dinitrotoluene	606-20-2	male reproductive toxicity	Used in organic synthesis, manufacture of dyes and explosives	NIOSH (1985) US EPA (1986a)
Technical Grade Dinitrotoluene	---	female reproductive toxicity male reproductive toxicity	Used in organic synthesis and manufacture of dyes and explosives	NIOSH (1985)
Heptachlor	76-44-8	developmental toxicity	Pesticide	US EPA (1980, 1986b)
Methyl chloride	74-87-3	developmental toxicity male reproductive toxicity	Used in manufacturing of silicones and other chemical products	NIOSH (1984, 1994)

CARCINOGENS

Chloroprene (CAS No. 126-99-8)

Increased incidence of malignant tumors and combined malignant and benign tumors in male and female mice at multiple sites; increased incidence of combined malignant and benign tumors in male rats at multiple sites and in female rats.

NTP (1996a; 1996d) has concluded that there is clear evidence of the carcinogenic activity of chloroprene in male and female $B6C3F_1$ mice and in male and female F344/N rats.

NTP (1996a) exposed $B6C3F_1$ mice and F344/N rats to chloroprene by inhalation for two years. In rats, incidences of squamous cell papilloma or carcinoma of the oral cavity were significantly increased in mid- and high-dose males (0/50, 2/50, 5/50, 12/50 for controls, low-, mid- and high-dose groups, respectively) and in high-dose females (1/49, 3/50, 5/50, 11/50). The incidence of renal tubule adenoma or carcinoma was significantly increased in male rats (combined single and step sections: 1/50, 9/50, 6/50, 8/50). Although increases in female rats were not statistically significant, NTP noted the unusual finding of four renal tubule adenomas in high-dose females and one renal tubule carcinoma in a low-dose female. There were also statistically significant increases in thyroid follicular cell adenoma or carcinoma in male rats (0/50, 2/50, 4/49, 5/50). Although increases in thyroid follicular cell neoplasms in high-dose females were not significantly greater than in chamber controls, they did exceed the historical range for controls. In female rats, the incidence of mammary gland fibroadenoma was significantly greater in the mid- and high-dose groups compared to chamber controls (24/49, 32/50, 36/50, 36/50).

In both male and female $B6C3F_1$ mice, statistically significant increases in alveolar/bronchiolar neoplasms were observed in all dose groups except low-dose males (alveolar/bronchiolar adenoma or carcinoma combined: 13/26, 28/50, 36/50, 43/50 for males and 4/50, 28/49, 34/50, 42/50 for females). In addition, for all exposed males the incidences of hemangiosarcoma (3/50, 13/50, 22/50, 19/50) and combined hemangioma or hemangiosarcoma (3/50, 14/50, 23/50, 21/50) were significantly greater than in controls. In females, significant increases were also observed in hemangiosarcoma (4/50, 6/50, 17/50, 5/50) and combined hemangioma or hemangiosarcoma (4/50, 6/50, 18/50, 8/50). In mid- and high-dose male mice, there were also statistically significant increases in tumors of the Harderian gland (combined adenoma/carcinoma: 2/50, 5/50, 10/50, 12/50) and renal tubule adenoma (combined single and step sections: 0/50, 2/49, 3/50, 9/50). In females, there were statistically significant increases in hepatocellular carcinoma (5/50, 11/49, 14/50, 19/50); in mammary gland carcinoma (3/50, 4/50, 7/50, 12/50); in sarcoma of the skin (0/50, 11/50, 11/50, 18/50); in mesentery sarcoma (0/50, 4/50, 8/50, 3/50) and in Harderian gland adenoma (1/50, 3/50, 3/50, 8/50). Additionally, increased incidences of neoplasms of the forestomach in both males and females and of Zymbal's gland in females were attributed to chloroprene exposure.

These findings were published in a draft technical report and were subsequently reviewed by an external advisory committee in a public meeting and accepted at the December 11-12, 1996 NTP Technical Reports Review Subcommittee Meeting, as reported in the *Summary Minutes* for that meeting (NTP, 1996d).

Cobalt sulfate heptahydrate (CAS No. 10026-24-1)

Increased incidence of combined malignant and benign pulmonary tumors in male and female mice and female rats.

NTP (1996b; 1996d) has concluded that there is clear evidence of carcinogenic activity of cobalt sulfate heptahydrate in male and female $B6C3F_1$ mice and in female F344/N rats.

NTP (1996b) exposed $B6C3F_1$ mice and F344/N rats to cobalt sulfate heptahydrate via inhalation for two years. Alveolar/bronchiolar neoplasms were observed in both species. In mice, statistically significant incidences in alveolar/bronchiolar adenoma or carcinoma (combined) were observed in high-dose males (11/50, 14/50, 19/50, 28/50 for chamber control, low-, mid- and high-dose groups, respectively) and in mid- and high-dose females (4/50, 7/50, 13/50, 18/50).

In female F344/N rats, statistically significant increases in the incidences of both alveolar/bronchiolar adenomas and carcinomas were observed (combined alveolar/bronchiolar adenoma or carcinoma or squamous cell carcinoma: 0/50, 3/49, 16/50, 16/50). The combined historical incidence of these tumors is 7/650. No alveolar/bronchiolar carcinomas have been observed in 650 historical controls, compared to 2/49, 6/50, 6/50 for female rats exposed to cobalt sulfate heptahydrate at low-, mid- and high-doses. Additionally, a statistically significant increase in pheochromocytoma was observed in high-dose female rats.

In high-dose male rats, the combined incidence of alveolar/bronchiolar neoplasms (7/50) was significantly greater than that in chamber controls (1/50). NTP (1996b) concluded that there was some evidence of carcinogenic activity of cobalt sulfate heptahydrate in male F344/N rats.

These findings were published in a draft technical report and were subsequently reviewed by an external advisory committee in a public meeting and accepted at the December 11-12, 1996 NTP Technical Reports Review Subcommittee Meeting, as reported in the *Summary Minutes* for that meeting (NTP, 1996d).

Fenoxycarb (CAS No. 72490-01-8)

Increased incidence of combined malignant and benign tumors in multiple strains of mice.

US EPA (1996a) has classified fenoxycarb as a B2 carcinogen based on sufficient evidence in animals. The relevant studies are described below.

Male and female CD-1 mice were administered fenoxycarb via diet for 80 weeks. The US EPA (1996a) determined that the highest dose used in this study was not adequate for determining carcinogenicity in either males or females. However, even at the administered doses, statistically significant increases in the incidences of alveolar/bronchiolar neoplasms (adenoma/carcinoma combined: 7/50, 13/50, 14/50, 20/50 for control, low-, mid- and high-dose groups, respectively) and Harderian gland adenomas (7/50, 9/50, 6/50, 13/46) occurred in male mice. For both lung neoplasms and Harderian gland tumors, the data demonstrated a statistically significant trend with increasing dose. No effect was observed in female mice. A second study conducted in another mouse strain is noted by US EPA (1996a) in the "Weight of Evidence Considerations" section of the report. Preliminary review of this study indicated significant increases in lung adenoma/carcinoma in both sexes as well as significant increases in hepatocellular adenoma/carcinoma in male mice.

US EPA (1996a) also considered the fact that fenoxycarb is structurally related to urethane, and urethane is a potential metabolite of fenoxycarb. Urethane similarly produces lung tumors in a multitude of mouse strains and Harderian gland tumors in several different strains of mice.

Oxythioquinox (CAS No. 2439-01-2)

Increased incidence of combined malignant and benign tumors in male mice and at multiple sites in female rats, including rare kidney tumors in female rats.

US EPA (1996b) has classified oxythioquinox as a B2 carcinogen based on sufficient evidence in animals. Exposure to oxythioquinox resulted in lung tumors in male NMRI mice, hepatocellular tumors in both sexes of F344 rats and rare kidney tumors in female F344 rats. The relevant studies are described below.

In one study oxythioquinox was administered to male and female NMRI mice via diet for 91 weeks. In male mice, there was a statistically significant increase in the incidence of alveolar/bronchiolar adenomas (6/59, 11/69, 16/67, 16/69 for control, low-, mid- and high-dose animals, respectively) and in alveolar/bronchiolar adenomas or carcinomas combined (18/60, 24/69, 30/67, 32/69). In female mice, the incidences of alveolar/bronchiolar carcinoma (3/40, 4/36, 4/27, 10/33) and combined carcinomas and adenomas (7/68, 10/69, 8/59, 15/66) were significantly increased in high-dose animals compared to controls. Due to high mortality, the doses in the mid- and high-dose groups were considered by the Agency to be excessive in female mice.

In a second study oxythioquinox was administered to male and female Charles River Fischer 344 rats via diet for two years. In males, there was a statistically significant increase in the incidence of hepatocellular adenomas in the high-dose group (0/50, 0/50,

3/49, 7/50 for control, low-, mid- and high-dose groups, respectively). In females, incidences of liver adenomas or carcinomas (combined) were significantly greater in high-dose animals compared to controls (0/48, 1/46, 3/56, 11/46). Incidences at the high doses exceeded historical control ranges for both males and females. Additionally, there was a statistically significant increase in kidney tubular epithelial neoplasms in high-dose females (combined adenomas/carcinomas: 0/48, 0/46, 4/46, 5/46). Although the increase was only marginally statistically significant ($p = 0.054$) at the mid-dose, US EPA (1996b) considered it biologically significant. The tumor type is regarded as rare. The Agency concluded that the highest dose in this study may have been slightly excessive, but noted there was no effect on survival. The Agency also noted that kidney tumors, considered to be rare, exceeded the historical control incidence at both the mid- and high-doses.

o-Phenylphenol (CAS No. 90-43-7)

Increased incidence of combined malignant and benign uncommon tumors to an unusual degree, with early onset in multiple studies in male rats.

US EPA (1994a) has classified *o*-phenylphenol as a Group B2 carcinogen based on sufficient evidence in animals. In 1987, sodium *o*-phenylphenate was identified by the International Agency for Research on Cancer as a Group 2B carcinogen and was listed under Proposition 65 on January 1, 1990. The relevant studies are described below.

In studies with F344/DuCrj rats, animals were treated with a pelleted diet of *o*-phenylphenol for 13 weeks (males and females) or 91 weeks (males only). In the 13-week study, transitional cell papillomas of the urinary bladder were observed in 6/12 males in the second highest dose group. No tumors were found in controls or in any other dose group. In the 91 week study, there were significant increases in both non-invasive carcinoma (0/24, 0/20, 15/24, 2/23 for control, low-, mid- and high-dose groups, respectively) and invasive carcinoma (0/24, 0/20, 5/24, 0/23) of the urinary bladder. The combined incidence of papilloma and carcinoma was 0/24, 0/20, 23/24, 4/23.

In another study, male F344/DuCrj rats were treated with *o*-phenylphenol or sodium *o*-phenylphenate in the diet for 26 weeks. Statistically significant increases in urinary bladder tumors (papillomas and carcinomas) occurred in rats treated with both *o*-phenylphenol (12/31) and with sodium *o*-phenylphenate (22/31). No tumors were found in control animals.

Primidone (CAS No. 125-33-7)

Increased incidence to an unusual degree of malignant liver tumors, including rare hepatoblastomas in male and female mice.

NTP (1996c; 1996d) has concluded that there is clear evidence of the carcinogenicity of primidone in male and female $B6C3F_1$ mice based on increased incidences of hepatocellular neoplasms in males and females. An increased incidence in thyroid gland follicular cell adenomas in males was also considered to be chemical related.

NTP (1996c) administered primidone to F344/N rats and $B6C3F_1$ mice in feed for two years. In both male and female mice, marked increases in the incidence of hepatocellular neoplasms were observed. In female mice, there were statistically significant increases in the incidences of hepatocellular adenoma and hepatocellular carcinoma in each dose group. The incidence of hepatocellular carcinoma/hepatoblastoma (combined) was 4/50, 12/50, 20/40, 39/50 for control, low-, mid- and high-dose groups, respectively. The combined incidence of hepatocellular adenoma/carcinoma/hepatoblastoma was 16/50, 42/50, 46/49, 50/50. In male mice, the incidences of hepatocellular adenoma, carcinoma and hepatoblastoma were also significantly greater for each dose group in comparison to controls (combined incidence of hepatocellular carcinoma/hepatoblastoma: 12/50, 39/50, 40/50, 39/50; combined incidence of hepatocellular adenoma/carcinoma/hepatoblastoma: 31/50, 49/50, 49/50, 46/50). There was also a statistically significant increase in thyroid follicular cell adenoma in high-dose male mice (0/49, 3/48, 3/50, 6/50).

No evidence of carcinogenic activity of primidone was found in female rats, but NTP concluded that there was equivocal evidence in male rats based on a marginal increase in thyroid gland follicular cell neoplasms (primarily adenomas) and a marginal increase in renal tubule neoplasms.

These findings were published in a draft technical report and were subsequently reviewed by an external advisory committee in a public meeting and accepted at the December 11-12, 1996 NTP Technical Reports Review Subcommittee Meeting, as reported in the *Summary Minutes* for that meeting (NTP, 1996d).

Thiodicarb (CAS No. 59669-26-0)

Increased incidence of combined malignant and benign tumors in male rats, female mice and, to an unusual degree, in male mice.

US EPA (1996c) has classified thiodicarb as a Group B2 carcinogen based on statistically significant increases in hepatocellular adenomas, carcinomas and combined adenoma/carcinoma in both sexes of the CD-1 mouse and statistically significant increases in testicular interstitial cell tumors in male Sprague-Dawley rats. The relevant studies are described below.

In the mouse study, CD-1 mice were administered thiodicarb for 97 weeks via diet. The combined incidence of hepatocellular adenoma/carcinoma in males was 8/44, 7/46, 14/49, 37/49 for control, low-, mid- and high-dose groups, respectively. In females, the incidence (of combined hepatocellular adenoma/carcinoma) was 1/48, 1/47, 3/45, 28/49. US EPA (1996c) noted that the highest dose may have been excessive based on effects on

the hematopoietic system and other signs of toxicity. Mortality was also increased in female mice. However, the Agency also noted there were adequate numbers of mice of both sexes available at the study termination to assess the carcinogenicity of thiodicarb. It was further noted that the overall dose selection was improper in that the highest dose was more than 10-fold that of the mid-dose; that there was a suggestive tumor response in the male mouse liver even at the mid-dose (considered inadequate for assessing the carcinogenicity of thiodicarb by the Agency); and that the tumor incidences were unusually high.

In the rat study, thiodicarb was administered to male and female Sprague-Dawley rats via diet for 104 weeks. There was a statistically significant increase in testicular interstitial cell tumors in high-dose males (5/49, 3/48, 3/48, 12/47). No effects were observed in female rats.

Vinclozolin (CAS No. 50471-44-8)

Increased incidence of combined malignant and benign tumors in multiple studies in male and female rats.

US EPA (1996d) has classified vinclozolin as a B2 carcinogen based on sufficient evidence in animals. Exposure to vinclozolin resulted in an increased incidence of testicular Leydig cell tumors (adenomas and carcinomas) and prostate adenomas in male rats and adrenal tumors (adenomas and carcinomas), ovarian adenomas and uterine carcinomas in female rats. The relevant studies are described below.

In its evaluation, US EPA (1996d) looked at one mouse study and two rat studies. In the mouse study, there was a significant increase in hepatocellular neoplasms in both sexes of the C57 mouse at the highest dose level. However, this dose level was considered excessively toxic, based on body weight gain reductions, leading the Agency to question the relevancy of the hepatocellular tumors in the mice.

In a 24-month carcinogenicity study in Wistar rats, statistically significant increases in the incidence of testicular Leydig cell tumors were observed at both mid- and high-doses (combined malignant and benign: 23/48, 25/49, 47/50, 49/50 for control, low-, mid- and high dose groups, respectively; malignant: 0/48, 0/49, 0/50, 2/50). There were also significant increases in prostate adenomas (0/48, 3/49, 7/50, 5/50) in both mid- and high-dose groups, and a significant increasing trend in liver adenomas (0/48, 1/49, 1/50, 3/50). In female rats, increases in benign ovarian sex cord stromal tumors occurred at all doses (4/39, 7/36, 10/45, 29/45). These increases were statistically significant for the high-dose group and of borderline significance for mid-dose animals ($p=0.053$). Historical control data from 1300 female Wistar rats indicates that this is an uncommon tumor (mean: 0.4% with a range of 0 to 2.0%). There were also increases in uterine adenocarcinoma (1/41, 0/27, 1/27, 7/47) and adrenal cortical malignant and benign tumors (1/42, 2/42, 1/47, 22/48) at the highest dose. US EPA (1996d) considered the highest dose in this study to be excessive and used mid-dose for assessing carcinogenicity. At the mid-dose level, US

EPA (1996d) found that vinclozolin exposure resulted in statistically significant increases in Leydig cell tumors (malignant and benign) and prostate adenomas in male rats and benign ovarian sex cord stromal tumors in female rats. It should be noted that US EPA (1996d), in concluding that vinclozolin induces cancer in animals, also took into account the induction of uterine carcinomas in female Wistar rats.

US EPA (1996d) also evaluated a 24-month chronic feeding study in Wistar rats. In this study, statistically significant increases in Leydig cell malignant and benign tumors occurred in male rats (11/20, 12/20, 17/20, 19/20, 20/20 for controls and 4 dose groups, respectively). There were also significant increases in hepatocellular carcinoma in high-dose males, and a statistically significant positive trend with increasing dose (0/20, 0/20, 1/20, 1/20, 9/20). In females adrenal cortical adenomas and carcinomas (combined) were increased (0/20, 0/20, 0/20, 1/20, 6/20), as were benign ovarian sex cord tumors (0/20, 0/20, 2/20, 4/20, 10/20). For this study US EPA (1996d) also considered the highest dose excessively toxic and used the next highest dose for assessing carcinogenicity.

US EPA (1996d) also noted that vinclozolin and/or its metabolites are structurally related to several pesticides and drugs (and/or their metabolites) that also cause Leydig cell hyperplasia/tumors and ovarian tumors.

REPRODUCTIVE TOXICANTS

Di(2-ethylhexyl)phthalate (DEHP) (CAS No. 117-81-7)

Male reproductive toxicity **has been evidenced in experimental animals by testicular atrophy and reduced fertility.**
Developmental toxicity **has been manifested by increased frequencies of morphological abnormalities and increased embryolethality in experimental animals.**

NIOSH (1990) concluded that: "DEHP can cause testicular damage in rats. ...There is evidence that DEHP and its metabolite MEHP are teratogenic and embryolethal to rodents. ... Based on animal data it can be concluded that DEHP is carcinogenic and teratogenic. Due to a lack of human data the degree of risk to humans can not be evaluated, but DEHP should be considered as potentially carcinogenic and teratogenic to humans."

NIOSH (1990) reviewed numerous studies conducted in rats, mice and hamsters that provide evidence that DEHP causes male reproductive toxicity. Testicular atrophy was observed in multiple studies in rats, in one study in mice, in another in hamsters. Reduced fertility was observed in two studies in mice. NIOSH (1990) also reviewed several studies in rats and mice that provide evidence that DEHP causes developmental toxicity. Increased embryolethality and increased morphological abnormalities were observed in multiple studies in rats and mice treated with DEHP.

2,4-Dinitrotoluene (CAS No. 121-14-2); 2,6-Dinitrotoluene (CAS No. 606-20-2); Technical Grade Dinitrotoluene (TDNT)

Male reproductive toxicity **has been manifested as testicular atrophy and decreased spermatogenesis in experimental animals exposed to TDNT, 2,4-DNT, or 2,6-DNT.** ***Female reproductive toxicity*** **has been manifested as non-functioning ovaries in mice exposed to TDNT.**

The National Institute for Occupational Safety and Health (NIOSH, 1985) concluded that: "Data from animal studies using TDNT or 2,6-DNT which show reduced spermatogenesis, aspermatogenesis, or testicular atrophy in exposed dogs, rats, and mice and nonfunctioning ovaries in TDNT-exposed mice indicate a potential for adverse reproductive effects from exposure to these compounds." The Agency's recommendations include the statement that, "…a reproductive hazard may exist for workers exposed to TDNT or 2,6-DNT. Testicular atrophy, decreased spermatogenesis, or aspermatogenesis seen in three species of experimental animals exposed to TDNT or 2,6-DNT and nonfunctioning ovaries in mice exposed to TDNT form the basis for this concern." .

In the Executive Summary of *the Health and Environmental Effects Profile for Dinitrotoluene*, US EPA (1986a), stated that, "An assessment of the data generated by genetic and reproductive toxicity studies suggest that while 2,4- and 2,6-DNT can produce testicular damage, they do not appear to be genetically active in male germ cells. … Chronic and subchronic toxicity studies have revealed that the blood, liver, testis, and neuromuscular system are the primary organs affected by the DNTs." In reaching this conclusion, the Agency reviewed and summarized published studies demonstrating the adverse effects of 2,4- and 2,6- DNT on reproductive parameters in rats, mice, and dogs.

Heptachlor (CAS No. 76-44-8)

Developmental toxicity **has been manifested in experimental animals as reduced offspring viability.**

US EPA (1980) concluded, "Heptachlor has been shown to exhibit numerous toxicological effects in animal systems. …oral doses of heptachlor caused dominant lethal changes in male rats as demonstrated by an increase in the number of resorbed fetuses in intact pregnant rats. Heptachlor administered to rats caused a marked decrease in litter size, both in several litters of one generation as well as in successive generations." US EPA (1986b) concluded that, "A data gap exists in the area of teratology toxicity testing," but that, "Several reproduction studies have been reviewed by the Agency and were adequate to set a NOEL of 1.0 ppm for reproductive effects to the young, the liver being the target organ of effect. No further testing is required."

Methyl chloride (CAS No. 74-87-3)

Male reproductive toxicity **has been manifested in experimental animals as degeneration and atrophy of the seminiferous tubules.**
Developmental toxicity **has been manifested as morphological abnormalities in experimental animals.**

NIOSH (1984) concluded that: "Methyl chloride has been tested in mice and found to be a teratogen. Based on this evidence, NIOSH recommends…that methyl chloride be considered a potential occupational teratogen." NIOSH (1984) also stated that "…methyl chloride induced degeneration and atrophy of the seminiferous tubules in treated male rats." Methyl chloride is also identified as causing teratogenic and adverse reproductive effects in the 'NIOSH Pocket Guide to Chemical Hazards' (NIOSH, 1994).

REFERENCES

National Institute for Occupational Safety and Health (NIOSH, 1984). *Current Intelligence Bulletin 43: Monohalomethanes (Methyl Chloride CH3Cl, Methyl Bromide CH3Br, Methyl Iodide CH3I).* US Department of Health and Human Services, Public Health Services, NIOSH.

National Institute for Occupational Safety and Health (NIOSH, 1985). *Current Intelligence Bulletin 44. Dinitrotoluenes (DNT).* US Department of Health and Human Services. Public Health Service. Centers for Disease Control. NIOSH.

National Institute for Occupational Safety and Health (NIOSH, 1990) *NIOH and NIOSH Basis for an Occupational Health Standard: Di (2-ethylhexyl)phthalate (DEHP).* US Department of Health and Human Services. Public Health Service. Centers for Disease Control. NIOSH.

National Institute for Occupational Safety and Health (NIOSH, 1994) *NIOSH Pocket Guide to Chemical Hazards.* US Department of Health and Human Services. Public Health Service. Centers for Disease Control. NIOSH.

National Toxicology Program (NTP, 1996a). *Toxicology and Carcinogenesis Studies of Chloroprene (CAS No. 126-99-8) in F344/N Rats and B6C3F$_1$ Mice (Inhalation Studies).* Board Draft. NTP Technical Report Series No. 467 NTIS Publication No. 96-3957. US Department of Health and Human Services, NTP, Research Triangle Park, NC.

National Toxicology Program (NTP, 1996b). *Toxicology and Carcinogenesis Studies of Cobalt Sulfate Heptahydrate (CAS No. 10026-24-1) in F344/N Rats and B6C3F$_1$ Mice (Inhalation Studies).* Board Draft. NTP Technical Report Series No. 471 NTIS Publication No. 96-3961. US Department of Health and Human Services, NTP, Research Triangle Park, NC.

National Toxicology Program (NTP, 1996c). *Toxicology and Carcinogenesis Studies of Primidone (CAS No. 125-33-7) in F344/N Rats and B6C3F$_1$ Mice (Feed Studies).* Board Draft. NTP Technical Report Series No. 476 NTIS Publication No. 96-3966. US Department of Health and Human Services, NTP, Research Triangle Park, NC.

National Toxicology Program (NTP, 1996d). S*ummary Minutes from Peer Review of Draft Technical Reports of Long-Term Toxicology and Carcinogenesis Studies by the Technical Reports Review Subcommittee on December 11-12, 1996.* NTP, Research Triangle Park, NC.

US Environmental Protection Agency (US EPA, 1980). *Ambient Water Quality Criteria for Heptachlor.* Office of Water Regulations and Standards; Criteria and Standards Division. Washington, D.C.

US Environmental Protection Agency (US EPA, 1986a). *Health and Environmental Effects Profile for Dinitrotoluene.* Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Office of Research and Development, US EPA, Cincinnati, OH.

US Environmental Protection Agency (US EPA, 1986b). *Guidance for the Reregistration of Pesticide Products Containing as the Active Ingredient Heptachlor.* US EPA, OPP, Washington DC.

US Environmental Protection Agency (US EPA, 1989a). *Pesticide Tolerance, Avermectin B1 and Its Delta-8,9-Isomer. Final Rule.* Federal Register Vol. 54, page 23209.

US Environmental Protection Agency (US EPA, 1989b). *Pesticide Tolerance; Avermectin B1 and Its Delta-8,9-Isomer. Final Rule.* Federal Register Vol. 54, page 31836.

US Environmental Protection Agency (US EPA, 1994a). *Memorandum: Carcinogenicity Peer Review of Orthophenylphenol (OPP) and Sodium Orthophenylphenol (SOPP).* Office of Prevention, Pesticides and Toxic Substances. August 24, 1994.

US Environmental Protection Agency (US EPA, 1994b). Proposed Rule: Addition of Certain Chemicals; Toxic Chemical Release Reporting; Community Right to Know. *Federal Register* **59**: 1788.

US Environmental Protection Agency (US EPA, 1994c). Final Rule: Addition of Certain Chemicals; Toxic Chemical Release Reporting; Community Right to Know. *Federal Register* **59**(229): 61432.

US Environmental Protection Agency (US EPA, 1996a). *Memorandum: Carcinogenicity Review Committee Review on Fenoxycarb.* Office of Prevention, Pesticides and Toxic Substances. April 1, 1996.

US Environmental Protection Agency (US EPA, 1996b). *Memorandum: Carcinogenicity Peer Review of Morestan (Oxythioquinox).* Office of Prevention, Pesticides and Toxic Substances. February 15, 1996.

US Environmental Protection Agency (US EPA, 1996c). *Memorandum: Carcinogenicity Peer Review of Thiodicarb.* Office of Prevention, Pesticides and Toxic Substances. June, 10, 1996.

US Environmental Protection Agency (US EPA, 1996d). *Memorandum: Carcinogenicity Peer Review of Vinclozolin (2nd).* Office of Prevention, Pesticides and Toxic Substances. September 18, 1966.

US Environmental Protection Agency (US EPA, 1996e). *Pesticide Tolerance; Avermectin B1 and Its Delta-8,9-Isomer. Final Rule.* Federal Register Vol. 61, No. 47, pages 9350-9352.